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## In vivo response to dynamic hyaluronic acid hydrogels.

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### Public Summary:

Tissue-specific elasticity arises in part from developmental changes in extracellular matrix over time, e.g. approximately 10-fold myocardial stiffening in the chicken embryo. When this time-dependent stiffening has been mimicked in vitro with thiolated hyaluronic acid (HA-SH) hydrogels, improved cardiomyocyte maturation has been observed. However, host interactions, matrix polymerization, and the stiffening kinetics remain uncertain in vivo, and each plays a critical role in therapeutic applications using HA-SH. Hematological and histological analysis of subcutaneously injected HA-SH hydrogels showed minimal systemic immune response and host cell infiltration. Most importantly, subcutaneously injected HA-SH hydrogels exhibited time-dependent porosity and stiffness changes at a rate similar to hydrogels polymerized in vitro. When injected intramyocardially host cells begin to actively degrade HA-SH hydrogels within 1week post-injection, continuing this process while producing matrix to nearly replace the hydrogel within 1month post-injection. While non-thiolated HA did not degrade after injection into the myocardium, it also did not elicit an immune response, unlike HA-SH, where visible granulomas and macrophage infiltration were present 1month post-injection, likely due to reactive thiol groups. Altogether these data suggest that the HA-SH hydrogel responds appropriately in a less vascularized niche and stiffens as had been demonstrated in vitro, but in more vascularized tissues, in vivo applicability appears limited.

### Scientific Abstract:

Tissue-specific elasticity arises in part from developmental changes in extracellular matrix over time, e.g. approximately 10-fold myocardial stiffening in the chicken embryo. When this time-dependent stiffening has been mimicked in vitro with thiolated hyaluronic acid (HA-SH) hydrogels, improved cardiomyocyte maturation has been observed. However, host interactions, matrix polymerization, and the stiffening kinetics remain uncertain in vivo, and each plays a critical role in therapeutic applications using HA-SH. Hematological and histological analysis of subcutaneously injected HA-SH hydrogels showed minimal systemic immune response and host cell infiltration. Most importantly, subcutaneously injected HA-SH hydrogels exhibited time-dependent porosity and stiffness changes at a rate similar to hydrogels polymerized in vitro. When injected intramyocardially host cells begin to actively degrade HA-SH hydrogels within 1week post-injection, continuing this process while producing matrix to nearly replace the hydrogel within 1month post-injection. While non-thiolated HA did not degrade after injection into the myocardium, it also did not elicit an immune response, unlike HA-SH, where visible granulomas and macrophage infiltration were present 1month post-injection, likely due to reactive thiol groups. Altogether these data suggest that the HA-SH hydrogel responds appropriately in a less vascularized niche and stiffens as had been demonstrated in vitro, but in more vascularized tissues, in vivo applicability appears limited.

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